Ketones or aldehydes and hemoglobin adducts

1: Cancer Epidemiol Biomarkers Prev 1998 Sep;7(9):817-21

4-Hydroxy-1-(3-pyridyl)-1-butanone-hemoglobin adducts as biomarkers of exposure to tobacco smoke: validation of a method to be used in multicenter studies.

Atawodi SE, Lea S, Nyberg F, Mukeria A, Constantinescu V, Ahrens W, Brueske-Hohlfeld I, Fortes C, Boffetta P, Friesen MD.

Unit of Gene-Environment Interactions, International Agency for Research on Cancer, Lyon, France.

Hemoglobin (Hb) adducts of 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB), a metabolite of two tobacco-specific nitrosamines [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N'-nitrosonornicotine], were measured as biomarkers of exposure to tobacco smoke as part of a study on genetic alterations and susceptibility to lung cancer among nonsmokers. HPB-Hb adducts were measured after collection of RBCs by Ficoll gradient in six collaborating centers, release of HPB by alkaline hydrolysis from Hb, clean-up by solid-phase extraction, and analysis of an electron-capturing derivative by gas chromatography-electron capture mass spectrometry. Prior to analysis of samples from study subjects, the reproducibility of this approach was validated in blood from donors. The coefficient of variation of reproducibility of paired aliquots from five samples ranged from 7 to 25%; the within-sample reproducibilities of four and eight aliquots were 4 and 16%, respectively. The study subjects consisted of 18 smokers and 52 never-smokers. HPB-Hb adduct levels were significantly higher (P = 0.02) in smokers (26 +/- 13 fmol HPB/g Hb) than in never-smokers (20 +/- 8 fmol HPB/g Hb). There was no difference between sexes. These results suggest that the level of HPB-Hb adducts, measured using a method modified to facilitate use in multicenter studies, can be a useful biomarker of exposure to tobacco smoke.

PMID: 9752992 [PubMed - indexed for MEDLINE]

2: Environ Health Perspect 1996 Dec;104 Suppl 6:1201-9

Chemistry of muconaldehydes of possible relevance to the toxicology of benzene.

BleasdaleC, Kennedy G, MacGregor JO, Nieschalk J, Pearce K, WatsonWP, GoldingBT. Department of Chemistry, University of Newcastle upon Tyne, United Kingdom.

(Z,Z)-Muconaldehyde reacted with primary amines to give N-substituted-2(2'-oxoethyl)-pyrroles, which were reduced to N-substituted-2-(2'-hydroxyethyl)-pyrroles by sodium borohydride. The pyrrole-forming reaction is exhibited by valine and its methyl ester, and is being developed with terminal valine in hemoglobin as a means of dose monitoring (Z,Z)-muconaldehyde, a putative metabolite of benzene. Reactions in aqueous solution between (Z,Z)-muconaldehyde and adenosine, deoxyadenosine, guanosine, or deoxyguanosine leading to pyrrole-containing adducts are described. The elucidation of the structures of the adducts was assisted by the study of reactions between (Z,Z)-muconaldehyde and both nucleoside derivatives and a model compound for guanosine. Reactions of (Z,Z)-muconaldehyde are complicated by its isomerization to (E,Z)- and (E-E)-muconaldehyde. The kinetics of this process have been studied in benzene, acetonitrile, and dimethylsulfoxide.

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3: Diabetes Care 1996 Nov;19(11):1233-6

Increase in circulating products of lipid peroxidation in smokers with IDDM.

Zoppini G, Targher G, Monauni T, Faccini G, Pasqualini E, Martinelli C, Zenari ML, Muggeo M.

Division of Endocrinology and Metabolic Diseases, University of Verona, Italy.

OBJECTIVE: To measure plasma malondialdehyde (MDA) concentration, a product of lipid peroxidation, both in IDDM patients and in healthy control subjects and to examine whether smoking has a negative impact on the plasma MDA levels in diabetic patients. RESEARCH DESIGN AND METHODS: Plasma total MDA concentration (as a thiobarbituric acid adduct by high-performance liquid chromatography) was measured in 56 young IDDM patients and in a group of 32 age-, sex-, BMI-, and smoking habit-matched healthy subjects. RESULTS: Plasma MDA concentration in IDDM patients was significantly higher than that in healthy control subjects (mean +/- SE: 0.95 +/- 0.03 vs. 0.54 +/- 0.03 mumol/l; P < 0.0001). After stratification by smoking status, it was seen that diabetic smokers had values of age, BMI, serum lipids, blood pressure, metabolic control, and diabetes duration and its chronic complications superimposable on those of their nonsmoking counterparts. Nevertheless, plasma MDA concentration was significantly higher in IDDM patients who smoked than in IDDM patients who didn't smoke (1.03 +/- 0.4 vs. 0.87 +/- 0.03 mumol/l; P = 0.002), without any sex difference with regard to MDA levels. CONCLUSIONS: These data show an increase in circulating products of lipid peroxidation in young diabetic smokers, thus further supporting the clinical importance of discouraging the initiation of smoking as well as promoting its cessation in people with IDDM.

PMID: 8908386 [PubMed - indexed for MEDLINE]

4: Eur J Biochem 1996 Aug 15;240(1):30-6

Structural characterisation of acetaldehyde adducts formed by a synthetic peptide mimicking the N-terminus of the hemoglobin beta-chain under reducing and nonreducing conditions.

Sillanaukee P, Hurme L, Tuominen J, Ranta E, Nikkari S, Seppa K.

Pharmacia & Upjohn, Diagnostics, Alcohol Related Diseases, Uppsala, Sweden.

This work was carried out to elucidate the structures resulting from acetaldehyde-induced modifications at the haemoglobin beta-chain N-terminal residues under different experimental conditions. A synthetic peptide (Val-His-Leu-Thr-Pro-Glu-Cys) of m/z 798, which represents the six N-terminal residues of the haemoglobin beta-chain N-terminus with an additional C-terminal cysteine, was used as a model compound. Peptide-acetaldehyde adducts were separated by reverse-phase HPLC. Fast-atom-bombardment MS and linked-scan (B/E) spectra were used to study adduct structures. Under nonreducing conditions at pH 7.4 (1:10 peptide/acetaldehyde molar ratio), two types of adducts of m/z 824 were formed, both with modifications at the N-terminal valine. These two adducts were shown to be a Schiff base, and a cyclic 2-methyl-imidazolidine-4-one. The 2-methyl-imidazolidine-4-one adduct was demonstrated to be formed via the Schiff base and to undergo dissociation gradually after 24 h. Reducing conditions at pH 7.4 (peptide /acetaldehyde molar ratio of 1:1 with 20 mM NaCNBH3) resulted in

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the formation of an adduct of m/z 826, which was shown to be an N-ethylated adduct of valine. A small amount of nonreduced adducts were also formed under these conditions. Reducing conditions at pH 9.0 (1:10 peptide/acetaldehyde molar ratio with 20 mM NaCNBH3) yielded two secondary, i.e. diethylated (m/z 854), products very rapidly. The cysteine residue of the peptide was not found to form an adduct with acetaldehyde under physiological pH.

PMID: 8797832 [PubMed - indexed for MEDLINE]

5: Alcohol Clin Exp Res 1995 Aug;19(4):939-44

Validated fluorimetric HPLC analysis of acetaldehyde in hemoglobin fractions separated by cation exchange chromatography: three new peaks associated with acetaldehyde.

Chen HM, Scott BK, Braun KP, Peterson CM.

Sansum Medical Research Foundation, Santa Barbara, California 93105, USA.

Stable hemoglobin-acetaldehyde adducts present in hemoglobin fractions separated by polyaspartic acid cation exchange chromatography were quantified by fluorimetric HPLC. The fluorescent species eluted from the HPLC was confirmed by mass spectrometry to be consistent with the expected product from reaction of acetaldehyde, 1,3-cyclohexanedione (CHD), and ammonium ion. Hemolysate (2.2 mM hemoglobin) was incubated in equivalent volumes of either phosphate-buffered saline or 5 mM acetaldehyde at 37 degrees C for 30 min and washed three times with H2O to remove free acetaldehyde and labile adducts before the injection of 14.7 mg hemoglobin onto the cation exchange column. Fluorimetric HPLC analysis of hemolysate samples either with or without in vitro reaction with acetaldehyde revealed that most acetaldehyde resides in the hemoglobin A0 fraction. The reaction with acetaldehyde in vitro resulted in a significant increase in fast-eluting minor hemoglobin species on cation exchange chromatography concomitant with increased acetaldehyde in the HbA1a+b, HbA1c, and HbA1-AcH fractions. We report three new cation exchange chromatographic peaks after reaction with acetaldehyde: HbA1-AcH-3, HbA1c-1, and HbA0-1. Each new peak was found to associate with a significant quantity of CHD-reactive acetaldehyde. These experiments provide additional evidence that stable adducts form between acetaldehyde and hemoglobin and that these adducts occur in multiple hemoglobin species separated by cation exchange chromatography. Further characterization and structural assignment of these species are warranted in view of their potential utility as markers for ethanol intake.

PMID: 7485842 [PubMed - indexed for MEDLINE]

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6: J Biol Chem 1995 May 12;270(19):11263-6

A structural assignment for a stable acetaldehyde-lysine adduct.

Braun KP, Cody RB Jr, Jones DR, Peterson CM.

Sansum Medical Research Foundation, Santa Barbara, California 93105, USA.

Acetaldehyde is the first oxidation product of ethanol in vivo. Lysine residues in proteins such as hemoglobin have been implicated as target structures for acetaldehyde adducts resulting from ethanol consumption. Although the presence of both stable and unstable acetaldehyde-hemoglobin adducts has been established, the structural characterization of the adducts has received relatively little attention. As a model for such adduct formation, we studied the peptide pentalysine in vitro. Pentalysine has several potential sites for adduct formation. The amino-terminal amine group as well as the epsilon-amine groups of each lysine side chain can serve as potential sites for modification by acetaldehyde. Mass spectrometry, nuclear magnetic resonance, and Raman spectroscopy were employed to demonstrate that acetaldehyde forms a stable linkage to lysine amine groups via a Schiff base.

PMID: 7744761 [PubMed - indexed for MEDLINE]

7: Alcohol Clin Exp Res 1995 Apr;19(2):314-9

Structural analysis of peptide-acetaldehyde adducts by mass spectrometry and production of antibodies directed against nonreduced protein-acetaldehyde adducts.

Lin RC, Smith JB, Radtke DB, Lumeng L.

Department of Medicine, Indiana University School of Medicine.

Acetaldehyde can form protein-acetaldehyde adducts (AAs) in vivo and may play a role in the genesis of alcoholic liver disease. The nature of the chemical modification of proteins by acetaldehyde in vivo has not been elucidated. In vitro, acetaldehyde can form reversible adducts including a Schiff's base with lysine (K) and imidazolidinone with terminal amino groups of proteins such as human hemoglobin (Hb). In this study, we used FAB/MS to analyze the products of peptide-AAs (pep-AAs) formed by incubating acetaldehyde with Hb peptides. We then used an octabranched multiple antigen peptide (MAP) system containing Hb peptide-AAs to raise antibodies. Three Hb peptides [i.e., 8-pep consisting of 8 residues (V1HLTPVEK8) at the N-terminus of beta-chain of human sickle-cell Hb, 11-pep-gly consisting of 11 residues (G56NPKVKAHGKK66) in a segment of beta-chain rich in lysine, and 11-pep-pro that consists of the same sequence as 11-pep-gly, except G56 was replaced by proline (P)] were incubated with 1 mM acetaldehyde at 4 degrees C for 7d without NaCNBH3 (nonreduced conditions). Analysis by FAB/MS showed that 8-pep formed an imidazolidinone at the N-terminal valine, 11-pep-gly formed a Schiff's base and imidazolidinone at the N-terminus, whereas 11-pep-pro that lacks a free alpha-amino group formed only a Schiff's base at K59. By contrast, incubation of these Hb peptides with 250 mM acetaldehyde and NaCNBH3 at 37 degrees C for 1 hr (reduced conditions) produced mono- and diethylated modifications of all available K residues, as well as the N-terminal amino group.(ABSTRACT TRUNCATED AT 250 WORDS)
PMID: 7625563 [PubMed - indexed for MEDLINE]

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8: Anal Biochem 1995 Jan 1;224(1):323-9

Separation of hemoglobin acetaldehyde adducts by high-performance liquid chromatography-cation-exchange chromatography.

Itala L, Seppa K, Turpeinen U, Sillanaukee P.

Biomedical Research Center, Alko Limited, Helsinki, Finland.

A HPLC-based method was developed to provide a simple way to study changes to hemoglobin induced by acetaldehyde in vitro. This method distinguished 18 human hemoglobin fractions including a new acetaldehyde-induced fraction HbA1ach3. The method consists of a Poly CAT A cation-exchange column and a stepwise salt and pH gradient, with a total analysis time of 31 min. The formation of acetaldehyde adducts was studied by incubation of hemoglobin with different Ach concentrations (5-1000 microM) and different incubation times (0-48 h). Physiological (5-250 microM) Ach concentrations induced increases mainly in 3 known fractions: HbA1ach1, HbA1prec, and HbA1d3; plus, it caused the formation of a new fraction, HbA1ach3. The specificity of the changes to acetaldehyde was studied by incubation of hemoglobin with glucose and acetylsalicylic acid. HbA1ach3 was the only acetaldehyde-induced hemoglobin fraction which was not also increased by glucose and acetylsalicylic acid treatment. The formation of HbA1ach3 showed a dose and time dependence on acetaldehyde incubations. Dialyzation and reduction experiments showed that HbA1ach3 is a stable adduct of hemoglobin, and incubation with purified HbA0 showed that HbA1ach3 is an adduct of HbA0. The within-run and between-run coefficients of variation for HbA1ach3 (0.83% of total hemoglobin) were 10.8 and 15.1%, respectively, and the analytical recovery was 82-97%. These results indicate that in addition to the new, acetaldehyde-specific fraction HbA1ach3, several other types of hemoglobin adducts were formed with acetaldehyde. The current method might be useful in clarifying the relationships between hemoglobin and acetaldehyde in vitro.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 7710090 [PubMed - indexed for MEDLINE]

9: Clin Investig 1994 May;72(5):364-71

Biomonitoring of hemoglobin adducts: aromatic amines and tobacco-specific nitrosamines.

Falter B, Kutzer C, Richter E.

Walther Straub-Institut fur Pharmakologie und Toxikologie, Ludwig-Maximilians-Universitat Munchen, Germany.

A new analytical procedure has been developed for the simultaneous determination of human hemoglobin adducts from aromatic amines and tobacco-specific nitrosamines. These tobacco-related hemoglobin adducts were determined in nonsmokers, smokers, and users of nasal snuff. Adducts from aminobiphenyl compounds are good biomarkers of exposure to tobacco smoke; they are not elevated in users of nasal snuff. However, a significant contribution of environmental exposure to aromatic amines and/or the corresponding nitroaromatics makes it difficult to evaluate passive exposure to tobacco smoke. The best biomarkers for exposure to tobacco smoke should in theory be adducts arising from tobacco-specific nitrosamines. The common adduct from

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N'-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone releases 4-hydroxy-1-(3-pyridyl)-1-butanone from hemoglobin upon mild alkaline hydrolysis and only marginal differences are found in the adduct level in smokers and nonsmokers. The reason for this observation is not yet understood and is currently under investigation. However, the adduct formed by tobacco-specific nitrosamines is well suited for the detection of oral and nasal tobacco use. Only by simultaneous determination of both adducts formed by aromatic amines and tobacco-specific nitrosamines is it possible to differentiate between nonsmokers, smokers, and nasal snuff users.

PMID: 8086771 [PubMed - indexed for MEDLINE]

10: Alcohol Alcohol Suppl 1994;2:509-13

The separation of hemoglobin-acetaldehyde adducts by cation exchange chromatography: a brief history.

Itala L, Sillanaukee P.

Biomedical Research Center, Alko Ltd, Helsinki, Finland.

Screening for alcohol abuse in its early phase, and the diagnosis of alcohol-related organ damage by laboratory tests in clinical settings, have often been unreliable. Protein-acetaldehyde adducts may be helpful in trying to solve this problem and hemoglobin, with its acetaldehyde adducts, appears to be a suitable model for studying protein-acetaldehyde adducts as condensation products of acetaldehyde, a harmful metabolite of ethanol. The modification by acetaldehyde alters the chromatographic properties of the hemoglobin molecule, producing a modified form that can be separated from other hemoglobin forms by cation exchange chromatographic techniques. The methods for the separation of hemoglobin acetaldehyde adducts have been improved in recent years, allowing us today to detect in vitro changes in hemoglobin caused by "physiological" concentrations of acetaldehyde and raising the possibility of developing a method suitable for clinical detection of hemoglobin acetaldehyde adducts.

Publication Types:
Historical Article
Review
Review, Tutorial

PMID: 8974376 [PubMed - indexed for MEDLINE]

11: Methods Enzymol 1994;231:657-67

Tobacco-specific nitrosamine-hemoglobin adducts.

Hecht SS, Carmella SG, Murphy SE.

American Health Foundation, Valhalla, New York 10595.

PMID: 8041285 [PubMed - indexed for MEDLINE]

Source: https://www.industrydocuments.ucsf.edu/docs/xqnx0001

12: Environ Health Perspect 1993 Mar;99:187-9

Mass spectrometric analysis of tobacco-specific hemoglobin adducts.

Schaffler G, Betz C, Richter E.

Walther Straub-Institut fuer Pharmakologie und Toxikologie, Muenchen, Germany.

Hemoglobin adducts of the common metabolite of the tobacco-specific nitrosamine (TSNA) 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB) and of 4-aminobiphenyl (4-ABP) were quantified in blood samples from smokers and nonsmokers to test their suitability for biomonitoring tobacco smoke exposure. Additionally, TSNA adducts were measured in nasal snuff users. Mild alkaline treatment of hemoglobin releases 4-ABP and HPB, which were analyzed in parallel by capillary gas chromatography with electronic impact or negative ion chemical-ionization mass spectrometry (EI- or NICI-GC-MS). Samples of snuff users showed high levels of HPB adducts not correlated with the amount or type of snuff used. HPB concentrations in smokers and nonsmokers, however, were much lower, with no group-specific differences detectable. In contrast, 4-ABP adduct levels were much higher in smokers than in nonsmokers, confirming the significant difference between these two groups reported by others.

PMID: 8319620 [PubMed - indexed for MEDLINE]

13: Chem Biol Interact 1992 Jun 15;83(1):55-63

Determination of hemoglobin adducts from aldehydes formed during lipid peroxidation in vitro.

Kautiainen A.

Department of Radiobiology, Arrhenius Laboratories for Natural Sciences, Stockholm University, Sweden.

This study was performed in order to investigate the formation of hemoglobin (Hb) adducts from some aldehydes, known to be formed during the peroxidation of polyunsaturated fatty acids. Hb was reacted in vitro with aldehydes followed by reduction of hemolysate with sodium borohydride and isolation of globin. Using the N-alkyl Edman method, globin samples were derivatized with pentafluorophenyl isothiocyanate for specific splitting off of N-substituted N-terminal valines. Adducts formed were then characterized by gas chromatography mass spectrometry using different ionization techniques. It was shown that adducts from saturated aldehydes were Schiff bases and those from alpha,beta-unsaturated aldehydes were mixtures of Schiff bases and 1,4-addition products. Aldehyde adducts were also measured in Hb from erythrocytes induced for lipid peroxidation. Incubation of the erythrocytes in presence of arachidonic acid led to increased levels of adducts.

PMID: 1643668 [PubMed - indexed for MEDLINE]

Source: https://www.industrydocuments.ucsf.edu/docs/xqnx0001

14: Cancer Res 1992 May 1;52(9 Suppl):2698s-2701s

DNA and hemoglobin adducts as markers of metabolic activation of tobacco-specific carcinogens.

Foiles PG, Murphy SE, Peterson LA, Carmella SG, Hecht SS.

Division of Chemical Carcinogenesis, American Health Foundation, Valhalla, New York 10595.

Lung cancer is now the leading cause of excess mortality among smokers in the United States. The ability to identify smokers with the greatest risk of developing lung cancer would be an important step in reducing lung cancer mortality. Tobacco-specific nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N'-nitrosonornicotine are important carcinogens in tobacco smoke. These carcinogens require metabolic activation to exert their carcinogenic effects. Methods are described for the measurement of DNA and hemoglobin adducts formed by the metabolites of these nitrosamines. Preliminary evidence is presented that shows that a subpopulation of smokers have elevated levels of DNA and hemoglobin adducts of tobacco-specific nitrosamines. Further work is in progress to test the hypothesis that smokers with elevated levels of tobacco-specific nitrosamine adducts are at increased risk of developing lung cancer.

Publication Types:
Review
Review, Tutorial

PMID: 1563001 [PubMed - indexed for MEDLINE]

15: J Protein Chem 1991 Jun;10(3):345-58

Aldimine to ketoamine isomerization (Amadori rearrangement) potential at the individual nonenzymic glycation sites of hemoglobin A: preferential inhibition of glycation by nucleophiles at sites of low isomerization potential.

Acharya AS, Roy RP, Dorai B.

Albert Einstein College of Medicine, Department of Medicine, Bronx, New York 10461.

The relative roles of the two structural aspects of nonenzymic glycation sites of hemoglobin A, namely the ease with which the amino groups could form the aldimine adducts and the propensity of the microenvironments of the respective aldimines to facilitate the Amadori rearrangement, in dictating the site selectivity of nonenzymic glycation with aldotriose has been investigated. The chemical reactivity of the amino groups of hemoglobin A for in vitro reductive glycation with aldotriose is distinct from that in the nonreductive mode. The reactivity of amino groups of hemoglobin A toward reductive glycation (i.e., propensity for aldimine formation) decreases in the order Val-1(beta), Val-1(alpha), Lys-66(beta), Lys-61(alpha), and Lys-16(alpha). The overall reactivity of hemoglobin A toward nonreductive glycation decreased in the order Lys-16(alpha), Val-1(beta), Lys-66(beta), Lys-82(beta), Lys-61(alpha), and Val-1(alpha). Since the aldimine is the common intermediate for both the reductive and nonreductive modification, the differential selectivity of protein

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for the two modes of glycation is clearly a reflection of the propensity of the microenvironments of nonenzymic glycation sites to facilitate the isomerization reaction (i.e., Amadori rearrangement). A semiquantitative estimate of this propensity of the microenvironment of the nonenzymic glycation sites has been obtained by comparing the nonreductive (nonenzymic) and reductive modification at individual glycation sites. The microenvironment of Lys-16(alpha) is very efficient in facilitating the rearrangement and the relative efficiency decreases in the order Lys-16(alpha), Lys-82(beta), Lys-66(beta), Lys-61(alpha), Val-1(beta), and Val-1(alpha). The propensity of the microenvironment of Lys-16(alpha) to facilitate the Amadori rearrangement of the aldimine is about three orders of magnitude higher than that of Val-1(alpha) and is about 50 times higher than that of Val-1(beta). The extent of nonenzymic glycation at the individual sites is modulated by various factors, such as the pH, concentration of aldotriose, and the concentration of the protein. The nucleophiles--such as tris, glycine ethyl ester, and amino guanidine--inhibit the glycation by trapping the aldotriose. The nonenzymic glycation inhibitory power of nucleophile is directly related to its propensity to form aldimine. Thus, the extent of inhibition of nonenzymic glycation at a given site by a nucleophile directly reflects the relative role of pKa of the site in dictating the glycation at that site.(ABSTRACT TRUNCATED AT 400 WORDS)

PMID: 1910466 [PubMed - indexed for MEDLINE]

16: Carcinogenesis 1991 Jun;12(6):1097-102

In vivo hemoglobin dosimetry of malonaldehyde and ethene in mice after induction of lipid peroxidation. Effects of membrane lipid fatty acid composition.

Kautiainen A, Tornqvist M, Anderstam B, Vaca CE.

Department of Radiobiology, Arrhenius Laboratories for Natural Sciences, Stockholm University, Sweden.

Hemoglobin (Hb) adduct determination by the N-alkyl Edman method was used for in vivo dosimetry of endogenously formed malonaldehyde (MA) and ethene in mice fed diets with different fatty acid composition and induced for lipid peroxidation with carbon tetrachloride (CCl4). In order to amplify lipid peroxidation animals were pretreated with phenobarbital (PB) and the glutathione-depleting agent DL-buthionine-(S,R)-sulfoximine (BSO). Non-treated animals raised on different diets were used as controls. Lipid peroxidation products in liver were measured as 2-thiobarbituric acid reactive compounds (TBA-C). Livers from control mice fed a soya oil based diet (rich in polyunsaturated fatty acids, diet S) showed approximately 6.5-fold higher levels of TBA-C than those from animals raised on a coconut oil based diet (mostly saturated fatty acids, diet C). The level of adducts of MA to Hb, determined as N-(3-hydroxypropyl)valine, was approximately 1.5-fold higher in animals from diet S than in animals raised on diet C. The highest increases in the levels of TBA-C and MA adducts were obtained after a simultaneous treatment of the animals with PB, BSO and CCl4. The increases of TBA-C were 1.3-fold (diet C) and 1.7-fold (diet S). The corresponding increases of MA-Hb adduct levels were 1.3- and 1.6-fold respectively, indicating an increased susceptibility of mice fed diet S to lipid peroxidation. The level of adducts from ethene, determined as N-(2-hydroxyethyl)valine, was also higher in mice from diet S than in animals fed diet C, when all treatment groups were considered. The difference was, however, only slightly significant (P less than 0.02). No difference between control and CCl4-treated animals, with regard to

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the ethene-Hb adduct, was found. Our results validate the use of Hb dosimetry for monitoring the effects of factors known to influence lipid peroxidation induced in vivo.

PMID: 1670288 [PubMed - indexed for MEDLINE]

17: Carcinogenesis 1989 Nov;10(11):2123-30

Adducts of malonaldehyde and a few other aldehydes to hemoglobin.

Kautiainen A, Tornqvist M, Svensson K, Osterman-Golkar S.

Department of Radiobiology, Arrhenius Laboratories for Natural Sciences, University of Stockholm, Sweden.

A method for the determination of hemoglobin (Hb) adducts of malonaldehyde (MA), one of the main products of lipid peroxidation, was developed. The method was based on a sodium borohydride reduction of MA-adducts to stable 3-hydroxypropyl adducts and quantification of the adduct to the N-terminal valine of Hb by a modified Edman procedure. Background levels of approximately 0.2 and 3.8 nmol/g Hb were recorded in one human volunteer and in control mice, respectively. Increased adduct levels were observed in mice after induction of lipid peroxidation with carbon tetrachloride. The kinetics of the reaction of MA with Hb and the stability of adducts formed were studied in in vitro experiments. Based on the adduct levels in Hb and the rate constant for adduct formation, the concentration of free MA in erythrocytes in mice was estimated. The background levels of adducts of some other aldehydes in Hb were also measured and the possibility that these adducts are formed as artefacts was studied.

PMID: 2805232 [PubMed - indexed for MEDLINE]

18: Ukr Biokhim Zh 1988 Jul-Aug;60(4):51-7

[Various enzymatic and nonenzymatic pathways of acetaldehyde transformation]

[Article in Russian]

Zavodnik IB, Stepuro II, Ostrovskii IuM.

In blood acetaldehyde is bound to hemoglobin and serum albumin and interacts with low-molecular-weight components--cysteine, glutathione. The association constants for human serum albumin and human hemoglobin are about 30 M-1 and 410 M-1, respectively. The SH-groups of hemoglobin play an essential role in the interaction of protein with acetaldehyde. The reversible complexes of acetaldehyde with proteins can transform into stable adducts after long incubation with albumin, some other blood proteins but not with immunoglobulins. Acetaldehyde participates as a substrate in the reaction of acetoin formation in homogenates of different tissues. The rate of acetoin formation is about 15 +/- 3 mmol/min per 1 gram of the tissue and essentially increases in the presence of pyruvate.

PMID: 3188257 [PubMed - indexed for MEDLINE]

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19: J Biol Chem 1986 May 25;261(15):6811-21

Reaction of acetaldehyde with hemoglobin.

San George RC, Hoberman HD.

Acetaldehyde reacted with hemoglobin at neutral pH and 37 degrees C to form adducts that were stable to dialysis and that were not reduced by sodium borohydride. Hemoglobin tetramers having 2, 3, and probably 4 molar eq of bound aldehyde were isolated by cation exchange chromatography. The sites of attachment of the aldehyde were the free amino groups of the N-terminal valine residues of the alpha and beta chains of hemoglobin. Derivatization of the beta chains caused a greater increase in the acidity of the hemoglobin than did derivatization of the alpha chains. Derivatization of the beta chains was also preferred over that of the alpha chains. Acetaldehyde derivatives of the N-terminal octapeptide of hemoglobin S (beta sT-1 peptide), Val-Gly-Gly, and tetraglycine were formed readily, contained 1 M eq of acetaldehyde/mol of peptide, and were not reduced by sodium borohydride. In contrast, Ala-Pro-Gly failed to form a 1:1 adduct with acetaldehyde. 13C NMR analysis of the peptide adducts formed with [1,2-13C]acetaldehyde indicated that tetrahedral diastereomeric derivatives were produced. The 13C chemical shifts of the adducts formed between hemoglobin and [1,2-13C]acetaldehyde were identical to those of the peptide adducts although resonances from the individual diastereomeric adducts at each hemoglobin site could not be resolved. The results cited above as well as other evidence indicate that acetaldehyde reacts with the amino termini of hemoglobin to form stable cyclic imidazolidinone derivatives. An exchange of acetaldehyde residues between peptides was also documented.

PMID: 3700416 [PubMed - indexed for MEDLINE]

20: Proc Soc Exp Biol Med 1986 Jan;181(1):151-6

Differential modification of hemoglobin chains by acetaldehyde.

Nguyen LB, Peterson CM.

Acetaldehyde-hemoglobin adducts have been suggested as potential markers for alcohol consumption. These adducts were formed in vitro with [14C]acetaldehyde and separated into hemoglobin subunits by cation-exchange chromatography to examine the relative modification of the alpha- and beta-chains. The effect of varying concentrations of acetaldehyde on the relative amounts of polypeptide adducts and on the specific radioactivities of undissociated hemoglobin (Hb) following reaction with hydroxymercurybenzoate (HMB) was also studied. There were linear relationships (P less than 0.05) between increasing levels of [14C]acetaldehyde (0.0, 0.1, 0.2, 0.5 mM) and the radioactivities of the alpha- and one of the two beta-chain adducts (22, 25, 53 dpm/mg Hb and 151, 272, 626 dpm/mg Hb, respectively). Increases in radioactivities of a minor unidentified hemoglobin adduct fraction were also observed. The ratios of specific radioactivities of beta-to alpha-chain (8.8 +/- 1.2 SEM) did not vary with the concentrations of acetaldehyde. Although the amounts of undissociated hemoglobin following reaction with HMB did not increase with increasing concentrations of acetaldehyde, the significant increase of specific radioactivities of this fraction (152, 1967, and 6562 dpm/mg Hb for 0.1, 0.2, and 0.5 mM acetaldehyde,

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respectively) suggested possible crosslinks within the tetramer or dimer. The amino acid analysis of alpha- and beta-subunit adducts formed with 0.1 and 0.5 mM acetaldehyde showed that unreacted cysteine residues were more often detected at the higher acetaldehyde concentration consistent with the formation of cysteine adducts labile to acid hydrolysis or the shielding of cysteine residues in acetaldehyde-modified Hb against the subunit separation by HMB treatment. Thus acetaldehyde reacts differentially with the alpha- and beta-hemoglobin subunits and with the undissociated hemoglobin molecule.

PMID: 3945617 [PubMed - indexed for MEDLINE]

21: Prog Clin Biol Res 1985;183:19-30

Clinical implications of acetaldehyde adducts with hemoglobin.

Peterson CM, Nguyen LB.

Acetaldehyde has been found to form adducts with human hemoglobin, a portion of which (15-25%) are stable to dialysis. The reaction is nonenzymatic and occurs with purified hemoglobin A. As determined by incorporation of radioactivity, the amount of stable hemoglobin adducts formed is proportional to the amount of acetaldehyde to which hemoglobin is exposed, or to the number of intermittent pulses. Reaction of hemoglobin A with 3 to 30 mM acetaldehyde significantly increases the amount of minor hemoglobins recovered following chromatography on cation exchange resin. Acetaldehyde adducts with hemoglobin involve primarily the beta chain and at least three different amino acid residues (valine, lysine and tyrosine), and two modified residues (glucosyl-valine and glucosyl-lysine). The acetaldehyde appears to be reacting with the epsilon-amino group of lysine and alpha-amino group of valine probably through an initial Schiff's base reaction. The secondary amines of glycosylated valine or glycosylated lysine residues are also proposed to be at the sites of reaction with acetaldehyde. Disubstitution of amino groups is known to occur with hexose sugar (Schwartz, Gray 1977) and by analogy, acetaldehyde might also react with the secondary amine of glycosylated residues. Acetaldehyde adduct formation with tyrosine residues may involve either a nucleophilic attack by the third or fifth carbon of the phenolic ring, analogous to formaldehyde modification of proteins (Blass, Bizzini, Raynaud 1965) or alternatively by reaction with the hydroxyl group of tyrosine. Only a portion of the stable hemoglobin-acetaldehyde adducts which were stable to 24h of dialysis could be irreversibly fixed by sodium borohydride or cyanoborohydride reduction. A greater portion however appeared to be in a non-reducible (non-carbonyl, non-amino) form. Up to 45% of the dialysis stable adducts could be reduced by sodium cyanoborohydride and be hydrolyzed to amino acid adducts if given either sufficient reduction time (2-3 weeks at 22 degrees C) or increased temperature (1-2 days at 50 degrees C). An increase in reducible adduct recovery occurred in all 5 residues detected by amino acid analysis. This suggests that the adducts that are stable to acid hydrolysis form and reverse through a reducible (e.g. Schiff base) form but that most of the time the adducts occur in a non-reducible state. At present, assay systems are not available which can detect acetaldehyde adducts in the blood of humans consuming alcohol.(ABSTRACT TRUNCATED AT 400 WORDS)

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Review

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22: Proc Soc Exp Biol Med 1984 Nov;177(2):226-33

The effect of acetaldehyde concentrations on the relative rates of formation of acetaldehyde-modified hemoglobins.

Nguyen LB, Peterson CM.

The effect of various concentrations of acetaldehyde (0, 0.05, 0.1, 0.25, 0.5, 1.0, and 5.0 mM) on the relative rates of formation of hemoglobin acetaldehyde adducts detected in fractions eluted from cation exchange high-pressure liquid chromatography (HPLC) was investigated. When the hemoglobin and acetaldehyde mixtures were incubated at 37 degrees C for various time intervals up to 24 hr, increased amounts of HbA1c could be observed after 2 hr incubation with 1 mM or greater concentrations of acetaldehyde, or after 4 hr incubation with at least 0.5 mM acetaldehyde. An increase in the HbA1a + b fraction was not observed with 4 hr incubation time until the acetaldehyde level reached 1 mM. The HPLC method detected no difference in minor hemoglobins from alcoholic and normal subjects. Incubation of red blood cells at 37 degrees C for 1 hr with six consecutive pulses of 0.05 mM [14C]acetaldehyde showed no differences in the amounts of minor hemoglobins determined chromatographically at various pulse intervals. However, the measure of the 14C-label incorporation into hemoglobin showed that adducts eluting in the HbA1a+b fraction were formed at a faster rate than those eluting in the HbA1c or HbA0 fraction, respectively. The specific activities of the HbA1a+b fractions at 2, 4, and 6 pulses were 34, 128, and 949 cpm/mg hemoglobin; those of the HbA1c fraction were 15, 58, and 174 cpm/mg hemoglobin. This evidence of modification of hemoglobin by physiological levels of acetaldehyde from 14C-label incorporation suggests that an assay more sensitive than chromatographic separation of adducts might be clinically useful in detecting alcoholism or monitoring alcohol detoxification programs.

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23: Biochim Biophys Acta 1984 Jul 20;804(3):308-23

The effect of glyceraldehyde on red cells. Haemoglobin status, oxidative metabolism and glycolysis.

Thornalley PJ, Stern A.

Glyceraldehyde induces changes in the flux of glucose oxidised through the hexose monophosphate pathway, the concentrations of intermediates in the Embden-Meyerhoff pathway, the oxidative status of haemoglobin and levels of reduced and oxidised pyridine nucleotides and glutathione in red cells. Glyceraldehyde autoxidises in the cellular incubations, consuming oxygen and producing glyoxalase I- and II-reactive materials. Major fates of glyceraldehyde in red cells appear to be: (i) adduct formation with reduced glutathione and cellular protein; (ii) autoxidation and reaction with oxyhaemoglobin and pyridine nucleotides, and (iii) phosphorylation of D-glyceraldehyde and entry into the glycolytic pathway as glyceraldehyde 3-phosphate. The production of glycerol from glyceraldehyde by red cell L-hexonate dehydrogenase appears not to be a major reaction of glyceraldehyde in red cells. These results indicate that high concentrations of glyceraldehyde (1-50 mM) may induce oxidative stress in

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red cells by virtue of the spontaneous autoxidation of glyceraldehyde, forming hydrogen peroxide and alpha-ketoaldehydes (glyoxalase substrates). The implications of glyceraldehyde-induced oxidative stress for the in vitro anti-sickling effect of DL-glyceraldehyde and for the polyol pathway metabolism of glyceraldehyde are discussed.

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24: Proc Natl Acad Sci U S A 1983 Jun;80(12):3590-4

Reaction of glycolaldehyde with proteins: latent crosslinking potential of alpha-hydroxyaldehydes.

Acharya AS, Manning JM.

The Schiff base adducts of glyceraldehyde with hemoglobin undergo Amadori rearrangement to form stable ketoamine structures; this reaction is similar to the nonenzymic glucosylation of proteins. In the present studies the analogous rearrangement of the Schiff base adducts of glycolaldehyde with proteins has been demonstrated. However, the Amadori rearrangement of the Schiff base adduct produces a new aldehyde function, an aldoamine, which is generated in situ and is capable of forming Schiff base linkages with another amino group, leading to covalent crosslinking of proteins. Sodium dodecyl sulfate gel electrophoresis of the glycoaldehyde-RNase A adduct showed the presence of dimers, trimers, and tetramers of RNase A, demonstrating the crosslinking potential of this alpha-hydroxyaldehyde. The crosslinked products exhibited an absorption band with a maximum around 325 nm and fluorescence around 400 nm when excited at 325 nm. The crosslinking reaction, the formation of a 325-nm absorption band, and the development of fluorescence were prevented when the incubation was carried out in the presence of sodium cyanoborohydride. This finding indicates that the Amadori rearrangement that generates a new carbonyl function is a crucial step in this covalent crosslinking. Glycolaldehyde could be a bifunctional reagent of unique utility because its crosslinking potential is latent, expressed only upon completion of the primary reaction.

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25: J Clin Invest 1983 May;71(5):1215-23

Oxidant damage of the lipids and proteins of the erythrocyte membranes in unstable hemoglobin disease. Evidence for the role of lipid peroxidation.

Flynn TP, Allen DW, Johnson GJ, White JG.

Since unstable hemoglobins have been considered a source of reactive oxygen radicals, and oxidative membrane damage a prehemolytic event, we examined the erythrocyte membranes of six patients (three splenectomized) with hemoglobin Koln disease. In the hydrogen peroxide stress test, the patients' erythrocytes generated more than twice the malonyldialdehyde (a lipid peroxidative product) than control erythrocytes. Fluorescence spectra of lipid extracts of the patients' erythrocytes showed an excitation maximum at 400 nm and an emission maximum of 460 nm, characteristic of malonyldialdehyde lipid adducts. Two types of membrane polypeptide aggregates were found in the erythrocytes of the

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splenectomized patients. The first, which were dissociable by treatment with mercaptoethanol, contained disulfide-linked spectrin, band 3 and globin. The second, not dissociable by mercaptoethanol, had an amino acid composition similar to that of erythrocyte membranes and spectrin (unlike globin) and like that of aggregates produced by the action of malonyldialdehyde on normal erythrocyte membranes. Atomic absorption spectroscopy of hemoglobin Koln erythrocytes showed no increase in calcium content implying that these cross-links were not due to calcium-stimulated transglutaminase. Using a micropipette technique, we demonstrated that erythrocytes containing membrane aggregates from splenectomized patients were less deformable while aggregate-free erythrocytes from non-splenectomized patients had normal deformability. We conclude that the erythrocyte membranes in hemoglobin Koln disease show evidence of lipid peroxidation with production of malonyldialdehyde, and that the nondissociable membrane aggregates formed in this disease are likely cross-linked by malonyldialdehyde. Because the erythrocytes containing membrane aggregates from splenectomized patients with unstable hemoglobin disease show decreased membrane deformability, we hypothesize that this abnormality results in premature erythrocyte destruction in vivo.

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26: J Biol Chem 1983 Feb 25;258(4):2296-302

Schiff base adducts of glyceraldehyde with hemoglobin. Differences in the Amadori rearrangement at the alpha-amino groups.

Acharya AS, Sussman LG, Manning JM.

PMID: 6822561 [PubMed - indexed for MEDLINE]

27: J Clin Invest 1981 Feb;67(2):361-9

Acetaldehyde adducts with hemoglobin.

Stevens VJ, Fantl WJ, Newman CB, Sims RV, Cerami A, Peterson CM.

Clinical studies on the minor hemoglobins (hemoglobin Ala-c) have suggested that a novel adduct may form in people abusing alcohol. Such patients were found to have an elevated concentration of minor hemoglobins, but normal or subnormal amounts of glycosylated hemoglobin (hemoglobin A1c) as determined by radioimmunoassay, Acetaldehyde, a reactive metabolite of ethanol, was postulated to form adducts with hemoglobin A that change its chromatographic properties. At physiological concentrations, acetaldehyde was found to form adducts with hemoglobin that were stable to extensive dialysis for several days. The amount of hemoglobin adducts formed were a function of the concentration and number of exposures to acetaldehyde. The reaction of acetaldehyde with hemoglobin A produced chromatographic variants, some of which migrated in the hemoglobin A1a-c region. Analysis of stable acetaldehyde-hemoglobin adducts demonstrated that valine, lysine, and tyrosine residues of globin were sites of reaction. The acetaldehyde-modified amino acid residues appear to exist in interconvertible conformations, only one of which is reducible by sodium borohydride. The amount of these adducts was found to be significantly elevated in hemoglobin from

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alcoholics as compared with normal volunteers.

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28: J Biol Chem 1980 Aug 10;255(15):7218-24

Amadori rearrangement of glyceraldehyde-hemoglobin Schiff base adducts. A new procedure for the determination of ketoamine adducts in proteins.

Acharya AS, Manning JM.

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